

**We Claim:**

1. An isolated polypeptide comprising 42 or more contiguous amino acids from an amino acid sequence selected from SEQ ID NOs: 2 and 12.
- 5 2. An isolated polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2 and 12.
3. An isolated polynucleotide encoding a polypeptide of claim 1.
- 10 4. An isolated polynucleotide comprising a nucleotide sequence selected from SEQ ID NOs: 1 and 11.
5. A recombinant vector comprising the polynucleotide of claim 3.
- 15 6. A host cell comprising the vector of claim 5.
7. An antibody which specifically binds to a polypeptide of claim 1.
8. An antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 39-42.
- 20 9. A method for making a polypeptide comprising culturing a host cell of claim 6 under conditions in which the nucleic acid is expressed.
- 25 10. The method of claim 9 wherein the polypeptide is isolated from the culture.
11. A method for identifying an antagonist of NPC1L1 comprising:
  - (a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface, in the presence of a known amount of detectably labeled ezetimibe, with a sample to be tested for the presence of the antagonist; and
  - 30 (b) measuring the amount of detectably labeled ezetimibe specifically bound to the polypeptide;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced binding of the detectably labeled ezetimibe to the polypeptide, compared to what would be measured in the absence of such an antagonist.

5 12. A method for identifying an antagonist of NPC1L1 comprising:

(a) placing, in an aqueous suspension, a plurality of support particles, impregnated with a fluorescer, to which a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface are attached;

10 (b) adding, to the suspension, radiolabeled ezetimibe and a sample to be tested for the presence of the antagonist, wherein the radiolabel emits radiation energy capable of activating the fluorescer upon the binding of the ezetimibe to the polypeptide to produce light energy, whereas radiolabeled ezetimibe that does not bind to the polypeptide is, generally, too far removed from the support particles to enable the radioactive energy to 15 activate the fluorescer; and

(c) measuring the light energy emitted by the fluorescer in the suspension; wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced light energy emission, compared to what would be measured in the absence of such an antagonist.

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13. The method of claim 12 wherein the fluorescer is selected from yttrium silicate, yttrium oxide, diphenyloxazole and polyvinyltoluene.

25 14. A method of claim 11 wherein the ezetimibe is labeled with a radiolabel selected from  $^3\text{H}$  and  $^{125}\text{I}$ .

15. A method of claim 12 wherein the ezetimibe is labeled with a radiolabel selected from  $^3\text{H}$  and  $^{125}\text{I}$ .

30 16. A method for identifying an antagonist of NPC1L1 comprising:

(a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOs: 2, 4 and 12 or a functional fragment thereof on a cell surface with a detectably labeled sterol or  $5\alpha$ -stanol and with a sample to be tested for the presence of the antagonist; and

35 (b) measuring the amount of detectably labeled sterol or  $5\alpha$ -stanol in the cell;

wherein an NPC1L1 antagonist in the sample is identified by measuring substantially reduced detectably labeled sterol or 5 $\alpha$ -stanol within the host cell, compared to what would be measured in the absence of such an antagonist.

5 17. The method of claim 16 wherein the sterol or 5 $\alpha$ -stanol is detectably labeled with a radiolabel selected from  $^3\text{H}$  and  $^{125}\text{I}$ .

18. The method of claim 16 wherein the sterol is cholesterol.

10 19. A method according to claim 11 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

20. A method according to claim 12 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

15 21. A method according to claim 16 wherein the host cell is selected from a chinese hamster ovary (CHO) cell, a J774 cell, a macrophage cell and a Caco2 cell.

20 22. A mutant mouse comprising a homozygous mutation of endogenous, chromosomal *NPC1L1* wherein the mouse does not produce any functional NPC1L1 protein.

23. The mouse of claim 22 wherein the mouse exhibits a reduced serum sterol or 5 $\alpha$ -stanol level.

25 24. The mouse of claim 22 wherein the region of endogenous, chromosomal *NPC1L1* deleted corresponds to nucleotides 790-998 of the nucleotide sequence set forth in SEQ ID NO: 45.

30 25. An offspring or progeny of the mouse of claim 22 wherein the offspring or progeny has inherited a mutated *NPC1L1* allele of said mouse.

26. A method for screening a sample for an intestinal sterol or 5 $\alpha$ -stanol absorption antagonist comprising:

(a) feeding a sterol or 5 $\alpha$ -stanol-containing substance to a first and second mouse

35 comprising a functional *NPC1L1* gene and to a third, mutant mouse of claim 21;

(b) administering the sample to the first mouse but not the second mouse;

(c) measuring the amount of sterol or 5 $\alpha$ -stanol absorption in the intestine of said first, second and third mouse; and

(d) comparing the levels of intestinal sterol or 5 $\alpha$ -stanol absorption in said first, second  
5 and third mouse;

wherein the sample is determined to contain the intestinal sterol or 5 $\alpha$ -stanol absorption antagonist when the level of intestinal sterol or 5 $\alpha$ -stanol absorption in the first mouse is less than the amount of intestinal sterol or 5 $\alpha$ -stanol absorption in the second mouse.

10 27. The method of claim 26 wherein the sterol is cholesterol.

28. The method of claim 27 wherein the cholesterol is radiolabeled.

15 29. The method of claim 26 wherein the level of sterol or 5 $\alpha$ -stanol cholesterol absorption is determined by measuring the level of serum sterol or 5 $\alpha$ -stanol in the mice.

30. A method for inhibiting NPC1L1 mediated sterol or 5 $\alpha$ -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 11.

20 31. A method for inhibiting NPC1L1 mediated sterol or 5 $\alpha$ -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 12.

32. A method for inhibiting NPC1L1 mediated sterol or 5 $\alpha$ -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 16.

25 33. A method for inhibiting NPC1L1 mediated sterol or 5 $\alpha$ -stanol uptake, in a subject, by administering, to the subject, a substance identified by the method of claim 26.

34. A kit comprising:

30 (a) ezetimibe in a pharmaceutical dosage form; and

(b) information indicating that NPC1L1 is a target of ezetimibe.

35. The kit of claim 34 wherein the dosage form is a tablet comprising 10 mg ezetimibe.

36. The kit of claim 34 further comprising simvastatin in a pharmaceutical dosage form.

37. The kit of claim 36 wherein the simvastatin in pharmaceutical dosage form comprises 5 mg, 10 mg, 20 mg, 40 mg or 80mg simvastatin.

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38. The kit of claim 36 wherein the simvastatin in pharmaceutical dosage form and the ezetimibe in pharmaceutical dosage form are associated in a single pill or tablet.

39. A method for decreasing the level of intestinal sterol or 5 $\alpha$ -stanol absorption in a

10 subject comprising reducing the level of expression of *NPC1L1* in the subject.

40. The method of claim 39 wherein the subject is a mouse, rat or human.

41. The method of claim 39 wherein the level of expression of *NPC1L1* in the subject is

15 reduced by mutating *NPC1L1* in the subject.

42. The method of claim 39 wherein the sterol is cholesterol.

43. A method for identifying an antagonist of *NPC1L1* comprising:

20 (a) contacting a host cell expressing a polypeptide comprising an amino acid sequence selected from SEQ ID NOS: 2, 4 and 12 or a functional fragment thereof on a cell surface, in the presence of a known amount of a detectably labeled 2-azetidinone, with a sample to be tested for the presence of the antagonist; and

25 (b) measuring the amount of detectably labeled 2-azetidinone specifically bound to the polypeptide;

wherein an *NPC1L1* antagonist in the sample is identified by measuring substantially reduced binding of the detectably labeled 2-azetidinone to the polypeptide, compared to what would be measured in the absence of such an antagonist.

30 44. A kit comprising:

(a) a 2-azetidinone in a pharmaceutical dosage form; and

(b) information indicating that *NPC1L1* is a target of the 2-azetidinone.

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